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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,725	01/13/2000	Ajit Lalvani	SHP-PT045	6572

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/308,725	LALVANI ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see attached*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's preliminary amendments filed May 24, 1999, March 7, 2000, March 22, 2000, June 23, 2005 and August 5, 2005, are acknowledged. Claims 40-50 are pending and under examination. Applicant's letters requesting the status of the instant application are acknowledged. Any delay in the prosecution of this application is regretted.

Information Disclosure Statement

2. The Information Disclosure Statements filed May 24, 1999, June 23, 2005, August 5, 2005, August 30, 2005 and May 18, 2006, are acknowledged and have been considered in part, as indicated on the PTO-1449s. Copies of each statement are attached to this Office action.

Declaration

3. The declaration is defective. A new declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

In particular, the addresses of the inventors have been altered without being initialed and dated. There is no application data sheet to confirm the information entered in the declaration.

Specification

4. The specification is objected to because it lacks a brief description of the drawings. If such a description was added in a preliminary amendment, Applicant is invited to point out the amendment. Otherwise, correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 42 recites, "wherein a peptide derived from ESAT-6 of *M. tuberculosis* is presented to the T cells". The metes and bounds of the claim cannot be determined because the derived peptide's structure is unclear. The retained portion of the original ESAT-6 is not defined for the derived peptide. Suggested language to overcome this rejection is, "wherein an ESAT-6 peptide of *M. tuberculosis* is presented to the T cells".

Summary of the claimed invention and claims interpretation

6. The claims are drawn to a method of assay in which peptide-specific effector T-cells are enumerated, which method comprises:

a. providing a fluid containing fresh T cells, which have not been cultured *in vitro*, in contact with a surface carrying an immobilized antibody to interferon-γ (IFN-γ),

b. presenting to the T cells a T cell-activating peptide,

c. incubating the fluid to cause release of said IFN-γ, and

d. detecting release IFN-γ bound to said immobilized antibody to enumerate said peptide-specific effector T cells;

wherein incubation is continued for a time to permit IFN-γ release by only those T cells that have been pre-sensitized *in vivo* to the T cell-activating peptide and are capable of immediate effector function without the need to effect division/differentiation by in vitro culture in the presence of the T cell-activating peptide; and said method being applied to diagnosis or monitoring of infection with an intracellular pathogen. Specifically, the intracellular pathogen is selected from the group consisting of hepatitis B (HBV), hepatitis C (HCV), *M. tuberculosis*, *P. falciparum*, human immunodeficiency virus (HIV), and influenza virus. The T cell activating peptide is of 7-12 amino acid residues in length. The peptide is added to the T cell containing fluid, which is recognized by $CD8^+$ T cells. The peptide is a known epitope, more specifically, the peptide is the *M. tuberculosis* ESAT-6 peptide. *(Note that the term, "a known epitope", is interpreted as "an epitope". The preceding word, "known", imparts no meaning to the term "epitope". This is because an epitope is known to be an epitope. One would not be able to practice the invention without using "a known epitope". An epitope would not be available for use in the method if it was unknown. Applicant is invited to clarify the meaning of the term is the Office is interpreting the term differently from Applicant's specification.)* The T cells are peripheral blood mononuclear cells (PBMCs). Particularly, the T cells are taken from a patient known to be suffering, or to have suffered from, infection with an intracellular pathogen. The fluid mixture is incubated under non-sterile conditions. The incubation is continued for a time of 4 to 24 hours. The claimed assay in intended to monitor progress of HIV infection. The method is also

intended to monitor the effect of a vaccine. Intended uses are not claim limitations, as there are no active steps in the claims that indicate monitoring the progress or effect of an infection or vaccine.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40, 41, 43 and 46-50 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara"). The claims are summarized above. Hagiwara discloses the effect of HIV infection on the frequency of cytokine-secreting cells in human peripheral blood. Hagiwara uses sensitive and specific ELIspot assays to detect and enumerate PBMC secreting cytokines *in vivo*. Hagiwara's analysis focuses on cytokine-producing cells that actively participate in on-going immune responses in HIV-infected individuals. Hagiwara discloses that the number of cells producing IL-2, IFN-γ and IL-10 is lower in HIV-infected individuals than healthy controls (pages 127-128, bridging paragraph).

Hagiwara describes the ELIspot assays on page 128. The method of assay in which peptide-specific effector T-cells are enumerated, comprises:

a) providing PBMCs from HIV-infected subjects ("a fluid containing fresh T cells") which have not been cultured *in vitro*, in contact with a 96-well nitrocellulose-backed

microtiter plate coated with anticytokine antibodies ("a surface carrying an immobilized antibody to interferon-γ"),

b) stimulating the cells with a 1:100 dilution of phytohemagglutinin ("presenting to the T cells a T cell-activating peptide"),

c) incubating the fluid for 6 hours at 37°C in a humidified 5% CO_2 in air incubator ("incubating the fluid to cause release of said IFN-γ"), and

d) overlaying the wells with biotinylated anticytokine antibody for 2 hours; then washing the plates; then treating with a 1/300 dilution of avidin-conjugated alkaline phosphatase for 1 hour; then washing a final time, then visualizing the single cells secreting cytokine by adding a solution of BCIP-NBT to the plates, ("detecting release IFN-γ bound to said immobilized antibody to enumerate said peptide-specific effector T cells");

wherein incubation is continued for a time to permit IFN-γ release by only those T cells that have been pre-sensitized *in vivo* to the T cell-activating peptide and are capable of immediate effector function without the need to effect division/differentiation by *in vitro* culture in the presence of the T cell-activating peptide.

Phytohemagglutinin is a mitogen that activates T cells. Given the teachings of Hagiwara, the claimed invention is clearly anticipated.

8. Claims 40, 43, 46, 47, 49 and 50 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Klinman *et al.* (*Current Protocols in Immunology*, 1994, 6.19.1-1.19.8, "Klinman"). The claims are summarized above. Klinman discloses the ELIspot assay for detecting and enumerating cytokine-secreting murine and human cells. The protocol is described

in Figure 6.19.1. Klinman discloses the use of peripheral blood cells (page 6.19.4, entire page), and suggests that stimulation of the cells can occur prior to addition of the cells or during incubation on the plate. Klinman discloses that for standard ELIspot analyses, the stimuli can be added directly to the cells while in the nitrocellulose-backed microtiter plates. The cells are then incubated for 6 to 24 hours to allow for cytokine production, such as IFN-γ. The cytokine-secreting cells are then enumerated (page 6.19.5).

With regard to the intended uses of monitoring progress of HIV infection and monitoring the effect of a vaccine, the Office does not consider them to be limiting. Intended uses are not claim limitations, as there are no active steps in the claims that indicate monitoring the progress or effect of an infection or vaccine.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara"). The claims are summarized above. Hagiwara teaches the claimed method/protocol, but is silent on the embodiment wherein the fluid mixture (T cells and activating peptide) is incubated under non-sterile conditions. The specification does not define exactly what conditions are encompassed by "non-sterile conditions" during incubation.

Regardless, it would have been obvious to one of ordinary skill in the art to forego the benefits of sterile conditions during incubation, step (c) of the method. The method does not require that the results be of any particular quality or accuracy.

10. Claims 40, 43, 44 and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyahira *et al.* (*Journal of Immunological Methods*, 1995, 181:45-54, "Miyahira") in view of Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara"). The claims are summarized above. Miyahira discloses the quantification of antigen specific $CD8^+$ T cells specific for the epitope SYVPSAEQI of a rodent malaria antigen using an ELIspot assay. The mice were previously immunized with *Plasmodium yoelii.* Miyahira performed the ELIspot assay with a murine $CD8^+$ T cell clone, YA26, which recognizes a class I MHV restricted epitope (SYVPSAEQI) of the CD protein of *P. yoelii* (page 47, "Results"). After the antigen stimulation, IFN-γ secreted by $CD8^+$ T cells was measured and cells were enumerated. Miyahira does not disclose the use of fresh T cells that have not been cultured *in vitro*.

However, Hagiwara teaches that ELIspot results are divergent when studying PBMC that had been cultured and stimulated *in vitro*. While Hagiwara's disclosure is directed to cytokine production in HIV patients, the same concept applies to Miyahira's ELIspot. Hagiwara teaches that since the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed, inconsistent results from such studies are not unexpected (page 131, first column). Hagiwara chose an alternative strategy, which was to study cells actively secreting

cytokines in vivo. Hagiwara's technique monitored the pattern of cytokines produced by cells participating in ongoing immune responses in HIV-infected individuals.

It would have been obvious to incorporate Hagiwara's teachings into Miyahira's method. One would have been motivated to use fresh T cells in Miyahira's method in view of Hagiwara's teachings about how the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed and that inconsistent results from such studies are not unexpected. Given this teaching, one of ordinary skill in the art would have been motivated to reduce inconsistent results by using fresh T cells, rather than the cells used by Miyahira that were cultured *in vitro* prior to the ELIspot assay. One would have had a reasonable expectation of success that the use of fresh T cells in Miyahira's method would have worked because Hagiwara's method uses fresh T cells in an ELIspot assay.

11. Claims 40-43 and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Surcel *et al.* (*Immunology*, 1994, 81:171-176, "Surcel"), in view of Sørensen *et al.* (*Infection and Immunity*, 1995, 63(5):17170-1717, "Sørensen"). The claims are summarized above.

Surcel discloses Th1/Th2 profiles in tuberculosis, based on the proliferation and cytokine response of blood lymphocytes to mycobacterial antigens. "Proliferation and cytokine production profiles by blood mononuclear cells in response to in vitro stimulation with mycobacterial antigens were compared in patients with active tuberculosis and in sensitized healthy people", page 171, abstract. Surcel uses the ELIspot assay to measure effector T cells that produce IFN-γ. Surcel's method uses freshly isolated PBMC from patients with active tuberculosis. The cells are incubated in 96-well plates for 72 hours before transfer to anti-IFN-γ

antibody-coated nitrocellulose-bottomed plates in the presence of a mycobacterial antigen. The cells were then incubated for 20 hours and subsequently enumerated (page 172, second column, last three paragraphs). Surcel is silent on the ESAT-6 mycobacterial antigen.

However, Sørensen discloses the discovery of a low-molecular-mass T-cell antigen secreted by *Mycobacterium tuberculosis*. Sørensen teaches that ESAT-6 is a 6-kDa early secretory antigenic target. Sørensen discloses that native and recombinant ESAT-6 elicted a high release of IFN-γ from T cells isolated from memory-immune mice challenged with *M. tuberculosis* (abstract).

It would have been obvious to use ESAT-6 as the activating peptide in Surcel's ELIspot method. One would have been motivated to use ESAT-6 because it is a T cell epitope. Surcel's method is aimed at studying the relationships between epitope specificity and T cell function (page 172, first column, first paragraph). One of ordinary skill in the art would have been motivated to use Sørensen's antigen as the activating antigen in order to understand the relationship between the ESAT-6 specificity and T cell function. One would have had a reasonable expectation of success based on Sørensen's disclose that ESAT-6 elicted a high release of IFN-γ from T cells isolated from memory-immune mice challenged with *M. tuberculosis*. Therefore, the invention would have been obvious to one of ordinary skill in the art at the time of the invention given the teachings of Surcel and Sørensen.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

13. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 6/14/06

Stacy B. Chen
Primary Examiner
June 14, 2006